Noncoding RNAs link PARP1 to heterochromatin

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Noncoding RNAs link PARP1 to heterochromatin

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PARP1 is a member of the poly(ADP-ribose) polymerases (PARP) family and is the most abundant chromatin-associated protein (1–2 million copies/cell) after histones. PARP1 modifies proteins by adding multiple ADP-ribose units (PAR) of different length and complexity and has been implicated in many nuclear processes, acting as DNA damage sensor, modulator of chromatin structure and transcriptional regulator. However, compared with other chromatin regulatory enzymes, PARP1 is poorly understood.[1]

Much evidence exists to support a paradoxical dual contribution of PARP1 in transcription and chromatin regulation. Although PARP1 associates with the promoters of almost all actively transcribed genes and acts to exclude linker histone H1,[2] it only regulates a subset of the bound genes and has both positive and negative effects of transcription.[2] Moreover, PARP1 binds to and regulates repressive heterochromatic structures, such as telomeres,[3] centromeres[4] and human α-satellites.[5] PARP1-mediated parylation has the ability to induce chromatin decondensation and enhance transcription.[6] However, examples exist where PARP1 as co-activator does not require its enzymatic activity.[7] In addition, parylation mediated by PARP1 was implicated in the correct function of heterochromatic chromocenter and telomeric regions. An additional issue is the regulation of PARP1 activity. During genotoxic stress, binding of damaged DNA to the N-terminal domain activates PARP1 to produce PAR polymers and, hence, most studies to date have focused on PARP1 role in DNA repair.[1] Considerably less is known about the factors activating PARP1 under physiological conditions.

Recent studies of our group analyzed the function of PARP1 within the nucleolus, the cellular compartment where several hundreds of rRNA (rRNA) genes are located.[5] Each cell contains both euchromatic rRNA genes, which are competent for transcription, and transcriptionally silent heterochromatic rRNA repeats.[8] Thus, the analysis of PARP1 in the nucleolus allows determining whether PARP1 is implicated in the formation of euchromatic or heterochromatic structures at genes sharing the same sequences but displaying distinct transcriptional and epigenetic features. Our results showed that PARP1 specifically associates with the promoter of silent rRNA genes (**Fig. 1**). Binding of PARP1 to rDNA promoter occurs immediately after the replication of silent rDNA in mid-to-late S phase, implying a role for the re-establishing of heterochromatic structures after the passage of the replication fork. Recruitment of PARP1 to rDNA promoter is mediated by TIP5, the major subunit of the nucleolar repressive complex NoRC, which is responsible for rDNA heterochromatin formation.[8] PARP1-TIP5 association is mediated by the noncoding pRNA, an intergenic transcript necessary for correct NoRC function.[9] PARP1 specifically only parylates components of rDNA heterochromatin (i.e., PARP1, TIP5 and histones), and this activity is required for rDNA silencing. The association of pRNA with the PARP1 N-terminal domain and its ability to stimulate PARP activity suggest that RNA may also be implicated in other PARP1-mediated biological processes requiring PARP1 activation under physiological conditions. PARP1 binding and parylation of nascent rDNA chromatin is a transient event, indicating that PAR modifications are required only for a short time. There are several possibilities by which parylation can establish silent rDNA chromatin. PARP1 could covalently modify and activate proteins to initiate the rDNA silencing process (i.e., TIP5). Alternatively, histone parylation might destabilize nucleosomes to gain accessibility to the action of chromatin regulatory enzymes (i.e., DNMTs, HMTs). Moreover, histone parylation might facilitate the deposition of repressive modifications by docking chromatin enzymes. As a fraction of PARP1 associates with the second half of the rDNA coding region and is TIP5-independent, we also predict that PARP1 might play further roles in regulating additional nucleolar activities, such as elongation and rRNA processing. Recent advances in PAR-mass spectrometry and generation of PAR-histone antibodies will soon afford us with a better understanding of how the code of parylated histones and chromatin regulators is mechanistically interpreted.

Our results provided evidences of an active role of PARP1 and its enzymatic activity for the establishment and inheritance of heterochromatic structures, adding important insights of how epigenetic marks are transmitted during each cell cycle. These findings may also impact a proposed combination therapy with genotoxic agents and PARP1 inhibitors for tumor treatment.[1,3] Evidence shows that maintenance of silent rDNA chromatin is necessary for genome stability (ref. 10 and references herein). Thus, with the new data presented here one should be cautious concerning long-term effects. PARP1 inhibition might even trigger enhanced genomic instability, causing formation of further neoplasias or letting tumors become insensitive to PARP inhibition due to additional mutations.

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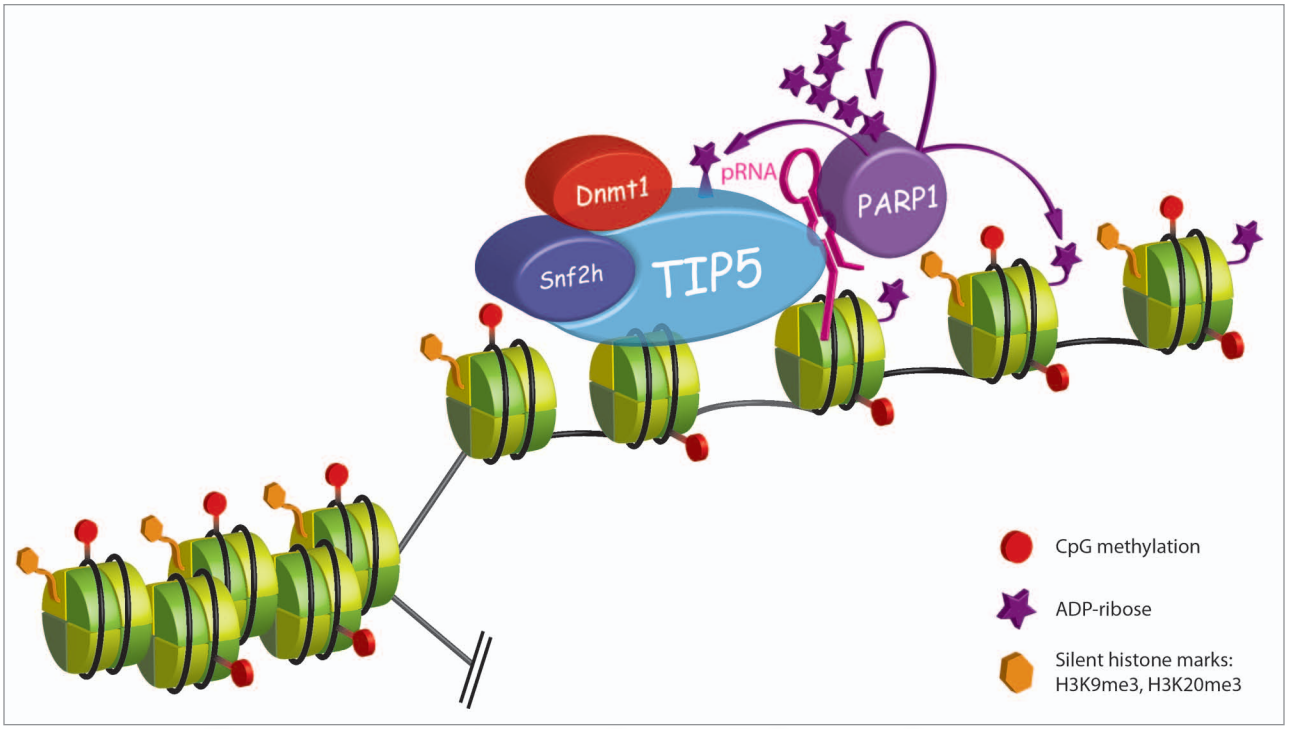

Figure 1. Model showing the inheritance of silent rDNA chromatin mediated by TIP5 (a component of NoRC complex), pRNA and PARP1. After the passage of the replication fork in mid S phase, TIP5-pRNA-PARP1 complex binds to rRNA genes. pRNA mediates the association of TIP5 with PARP1 and activates the enzymatic activity of PARP1 to parylate PARP1 itself, TIP5 or histones. PARP1 enzymatic activity facilitates formation of silent rDNA chromatin and transcriptional silencing.

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